

REMARKS

Claims 1-17 and 21-26 are pending. Claims 1, 2, 6 and 15 have been amended. Applicants respectfully request entry of the amendments, which merely deal with correction of typographical errors, or to clarify the invention. No new matter has been added. Applicants respectfully request reconsideration of the present rejections in view of the present remarks.

Rejections under 35 U.S.C. § 102

The Office rejected claims 1-5, 7-10 and 13 under 35 U.S.C. 102(b) as allegedly being anticipated by Okihara *et al.* (J. Macromol. Sci. Phy. (1991) B30, 119-140). In particular, the Office indicated that “[p]olymers of lactic acid and glycolic acid are water-soluble.” (Office Action, page 2). Applicants respectfully disagree. Nonetheless, to expedite prosecution, Applicants have amended claim 1 to specify a water soluble or water dispersible hydrophilic polymer. This amendment is supported at least on page 4, lines 25-34 and on page 5, lines 10-15. Thus, no new matter is added.

The Okihara reference does not anticipate the invention as claimed for at least the following reasons. First, the Okihara reference does not describe a hydrogel comprising a mixture of water soluble or water dispersible hydrophilic polymers in an aqueous system. As known in the art, hydrogels are polymeric networks which absorb and retain large amounts of water. (See, van Nostrum *et al.*, “ACS Symposium Series 846:129-141 (2003), previously submitted. A better copy is attached as Exhibit 1).

In contrast, no water is present in the stereocomplex described in Okihara. To prepare the stereocomplex in Okihara, uniaxial-drawn films using an equimolar mixed solution of poly(L-lactide) and poly(D-lactide) were prepared by placing a few drops of a 1 % solution of the poly(lactide) in p-xylene on a glass plate at 140 °C. Polymer melts remained after evaporation of the solvent, and drawn into a uniaxially oriented films. To raise the crystallinity of the stereocomplex, the films were annealed at 198 °C. Because the described system has no water

present, it is impossible to have a hydrogel present. (See also, Declaration of Wilhelmus Hennink, at ¶5, previously submitted).

Second, the Okihara reference is silent regarding water-soluble or water dispersible hydrophilic polymers. As the Office recognized, the components of the stereocomplex of Okihara are poly(L-lactide) and poly(D-lactide). (See, Office action mailed 4/7/04, at page 3, Remark 3). More specifically, the poly(lactides) have molecular weights ranging from 5,000 to 300,000. (See, Okihara, page 120).

As known to the skilled person, PLA is an aliphatic polyester consisting of repeating units of lactic acid or (2-hydroxypropionic acid). PLA has helix structures and bulky side chains, and is hydrophobic and impermeable to hydrophilic molecules. (See, Jonnalagadda *et al.*, AAPS PharmSci Tech 2000, 1(4) article 29, and Polymer Source online store catalog, attached at Exhibits 2 and 3, respectively). The water equilibrium concentration in saturated conditions is typically lower than 2 % by weight. PLA pellets are reported to have an absorption less than 8000 ppm (wt/wt). (See, Auras *et al.*, Effects of Water on the Oxygen Barrier Properties of Polyethylene Terephthalate and Poly(lactide) Films, attached at Exhibit 4).

Third, the Okihara reference is silent regarding substituted polymers. The poly(L-lactide) and poly(D-lactide) in the stereocomplex of Okihara are homopolymers. As known in the art, a “homopolymer” is a polymer having a chain structure in which all building units are of the same type. For example, the poly(lactide) in Okihara comprises repeating units of the lactide residue. (See, Okihara, Abstract and Introduction).

In contrast, the hydrogels of the invention as claimed comprises a mixture of substituted polymers that are not homopolymers. More particularly, the mixture comprises water soluble or water dispersible hydrophilic polymers substituted with a chiral oligomer or co-oligomer. For example, as shown in Figure 1, the hydrogel comprises a water soluble or water dispersible hydrophilic polymer (*e.g.*, dextran) substituted with lactide oligomers.

Because the Okihara reference fails to describe hydrogel compositions, the claims are not anticipated. Thus, Applicants submit that the claims as amended are novel, and respectfully request that this rejection be withdrawn.

The Office also rejected claims 1-10, 14 and 21-26 under 35 U.S.C. § 102(b), as allegedly being anticipated by Hennink *et al.* (WO 98/00170). In the Advisory action mailed February 8, 2005, the Office alleged that the “instant claims do not exclude hydrolysable bonds consisting of two interpenetrating networks.” The Office also indicated that “Hennink’s polymers encompass both isomers since no specific isomer is stated.” Applicants respectfully disagree.

First, WO 98/00170 fails to teach a hydrogel comprising a mixture of two water soluble or water dispersible hydrophilic polymers, let alone polymers substituted with a chiral substituent that is in essence complementary to each other. As previously indicated, poly(lactic acid) is a hydrophobic polymer. Similarly, poly(glycolic acid) is comprised of the same polyester building block, and is also hydrophobic. (See e.g., Material Safety Data Sheet, and Huh *et al.*, “PLGA-PEG Block Copolymers for Drug Formulations, each attached as Exhibit 5).

Furthermore, the hydrogel in the prior art comprises only of one polymer that is covalently bonded to each other through free radical polymerization of a crosslinkable group such as methacrylate. In Example 3, a methacrylated dextran is derivatized with L-lactide, a hydrolytically labile unit. By free radical polymerization using peroxydisulfate and TEMED as initiator, this methacrylated dextran coupled to an L-lactide is polymerized with itself (*i.e.*, another methacrylated dextran coupled to an L-lactide) via crosslinking of the methacrylate groups. (See Example 5).

In Example 4, a methacrylated dextran is derivatized with a glycolide. Unlike lactic acid which contains a chiral center and can therefore be in the L- or D- configuration, glycolic acid or hydroxyacetic acid does not contain an asymmetric carbon atom and is achiral. (See Merck index, attached at Exhibit 6). As known to the skilled person, achiral molecules do not have an enantiomer. Thus, unlike the invention as claimed, Hennink’s polymers described in WO 98/00170

does not comprise two polymers having chiral substituents that are in essence complementary to each other.

Second, WO 98/00170 only describes hydrogels comprising of covalently bonded interpenetrating networks. In Example 3 described above, no D-lactide substituent is present at all. Thus, the L-lactide substituent cannot be used as a chiral substituent of a first water soluble polymer, to interact noncovalently with a lactide substituent of a second water soluble polymer having opposite chirality.

Although the mechanism is not necessary to practice the invention as claimed, the formation of the gelled structure in the invention as claimed is believed to be caused by the interaction of the oligomerized monomers present on the hydrophilic polymers. More particularly, the oligomerized monomers of one chirality interacts noncovalently with that of oligomerized monomers of the opposite chirality. (See specification, at page 4, line 35 through page 5, line 15). Because there is no lactide substitute of opposite chirality in the prior art polymers, the polymers can only interact covalently through free radical polymerization of the crosslinkable group.

Because WO 98/00170 does not teach hydrogels comprising two polymers having chiral substituents that are in essence complementary to each other, wherein the groups on the polymers interact noncovalently, the invention as claimed is novel. Accordingly, Applicants respectfully request that this rejection be withdrawn.

Rejections under 35 U.S.C. § 103

The Office rejected claim 11 under 35 U.S.C. § 103(a), as allegedly being unpatentable under Hennink (WO 98/00170). Applicants respectfully disagree. Claim 11 depends from claim 1, and contains all the limitations in claim 1.

As previously indicated, the Hennink reference neither teaches nor suggests hydrogels comprising two polymers having chiral substituents that are in essence complementary to each other, wherein the groups on the polymers interact noncovalently. Thus, claim 11 is nonobvious

under Hennink and Applicants respectfully request that this rejection be withdrawn.

The Office also rejected claim 12 under 35 U.S.C. § 103(a), as allegedly being unpatentable under Okihara. In the Final Office action mailed 4/7/04, the Office indicated that “[it would have been obvious . . . to prepare a stereocomplex hydrogel composition that comprises any length monomers since Okihara appears to teach all lengths.” (Final Office action, page 5). Applicants respectfully disagree. Claim 12 depends from claim 1, and contains all the limitations in claim 1.

As previously indicated, the Okihara reference fails to describe hydrogels at all. The Okihara reference also fails to describe oligomeric lactic acids having an average chain length of 7-15 monomers. Contrary to the assertions of the Office, Okihara only teaches polylactides having molecular weights ranging from 5,000 to 300,000, and provides no motivation for the preparation of hydrogels from oligomeric lactic acids having an average chain length of 7-15 monomers. As known in the art, the physical properties of oligomeric and poly(lactic acid) are distinguishable. For example, oligomeric lactic acid chains with sufficiently low lactic acid content can be water soluble. In contrast, high molecular weight poly(lactic acid) chains are mostly insoluble in water. (See, Exhibit 1, page 133). Thus, claim 12 is nonobvious under Okihara and Applicants respectfully request that this rejection be withdrawn.

The Office also rejected claims 15-17 under 35 U.S.C. § 103(a), as allegedly being unpatentable under De Jong *et al.* (Macromolecules 31:6397-6402 (1998)), in view of Brannon-Peppas (Int. J. Pharm. 116: 1-9 (1995)). In particular, the Office indicated that “[t]he lactides and glycolides are water-soluble and thus De Jong and Brannon both disclose water-soluble [sic] polymers.” (Office Action, pages 4-5). Applicants again respectfully disagree. Nonetheless, to expedite prosecution, the process as claimed in claim 15 has been amended to specify the mixing of two mixtures in an aqueous system of water soluble or water dispersible hydrophilic polymers substituted with oligomers or co-oligomers partly formed from chiral monomers of opposite chirality.

The amended claims are not obvious under the cited prior art. De Jong fails to teach a process for preparing a hydrogel by mixing two mixtures in an aqueous system. De Jong teaches the synthesis of lactic acid oligomers from heating a neat mixture of lactide (*i.e.*, no solvent) and 2-(2-methoxyethoxy)ethanol as initiator, and subsequent addition of stannous octoate as catalyst. In particular, a mixture of L-lactide (or D-lactide) was stirred at 130 °C “until the lactide was molten.” (See, De Jong *et al.*, page 6399 at column 1). As previously indicated, it is impossible to obtain a hydrogel in the absence of water.

De Jong’s failure to teach the preparation of hydrogels as claimed is not remedied by Brannon-Pappas. Brannon-Pappas describes micro- and nanoparticulate delivery systems containing poly(lactic acid), poly(glycolic acid) or their copolymers. (See, Brannon-Pappas, Abstract). As previously indicated, poly(lactic acid) and poly(glycolic acid) are hydrophobic polymers. Furthermore, glycolic acid is an achiral molecule and therefore is incapable of forming enantiomers with opposite chiralities.

Thus, even if De Jong and Brannon-Pappas were combined, the combination fails to teach a process for preparing a hydrogel using an aqueous system. Accordingly, claims 15-17 are nonobvious under De Jong, in view of Brannon-Pappas, and Applicants respectfully request that this rejection be withdrawn.

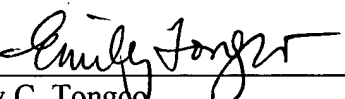
CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 313632001000. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

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